REMARKS

Claims 2, 5-8, 16, 18-21 and 23-24 are pending. No claims are amended.

Rejections Under 35 U.S.C. §103-Obviousness

Claims 2, 5-8, 16, 18-21 and 23-24 remain rejected as obvious over U.S. 5,183,659 to Timoney et al. ("Timoney"), in view of EP 0786518 to Hartford et al. ("Hartford"), and U.S. 5,597,807 to Estrada et al. ("Estrada"). The Examiner's specific points are addressed individually below.

1. The Examiner maintains that it would have been obvious for one of ordinary skill in the art to modify the unencapsulated *S. equi* vaccine in Timoney, from the teachings that saponin produces mucosal immunity (Estrada), in combination with disclosure that numerous adjuvants (including saponin) may be used in conjunction with an encapsulated, deletion mutant *S. equi* vaccine suitable for nasal administration (Hartford).

Applicants respectfully traverse this rejection for the following reasons. First, the disclosure by Hartford that eleven disclosed adjuvants can be used in a vaccine for an encapsulated *S. equi*, with a stated preference for LT (*E. coli* heat labile toxin) and CT (cholera toxin) for mucosal vaccines, does not, when combined with Estrada's disclosure of the suitability of saponins as adjuvants for administration orally, by inhalation, intradermally, intraperitoneally and intravenously injection (i.e., not nasally), provide the suggestion or motivation to specifically combine a saponin with an unencapsulated *S. equi* for nasal mucosal administration. This is especially so where Timoney makes no mention of using an adjuvant with his disclosed encapsulated *S. equi* vaccine.

Again, as iterated in previous responses, Hartford actually teaches away from the Timoney vaccine by the statement on page 2: "...the [prior art vaccine] has several drawbacks...the vaccine is based on a non-encapsulated strain...As a consequence, a vaccine based thereon would thus not protect against on apparent virulence factor i.e. the capsule." By this statement, Hartford teaches

away from the present invention, which also directed to a non-encapsulated vaccine. Where a reference teaches away from another reference, as does Hartford with respect to Timoney, it cannot be used in combination with that other reference to establish obviousness. See *In re Lundsford*, 148 U.S.P.Q. 721, 726 (CCPA 1966).

Further, Timoney discloses intranasal and oral administration of his *S. equi* vaccine free of any adjuvant. On the other hand, Estrada only teaches applying saponins to nasal mucosa to enhance adsorption of a drug or vaccine through mucous membranes, not to stimulate mucosal immunity. Moreover, the closest that Estrada comes to disclosing the use of saponin as an adjuvant in the nasal mucosa is by inhalation. Inhalation of an agent occurs via the mouth, into the lungs, which is clearly distinct from intranasal administration which occurs by direct application onto mucosal surfaces of the nasal cavity. Thus, there is no motivation in Estrada to combine saponin with an *S. equi* vaccine of Timoney, nor any motiviation in Timoney to use an adjuvant, much less a saponin, in the administration of *S. equi*.

In addition, while Estrada teaches that saponins are generally useful as adjuvants, and exemplifies saponin use only with CT and avidin as model antigens, there is no disclosure of the use of saponins as an adjuvant for an attenuated bacteria, much less with *S. equi*. To this end, as pertains to the instant application, where Estrada only mentions that mucosal administration of saponin enhances drug delivery, and not mucosal immunity, and where Timoney makes no mention of using an adjuvant to begin with, there can be no motivation to combine the two references with each other (or with Hartford, which in any event disparages Timoney) and arrive at the presently claimed invention.

Hartford does not remedy this deficiency to establish obviousness. Hartford *does* teach an *S. equi* vaccine, and discloses saponin (Quil A) as one adjuvant among numerous adjuvants. Although, Hartford teaches that the preferred mucosal adjuvants are CT and LT, not Quil A, Hartford does not exemplify use of any adjuvant in the experiments. Accordingly, there would have been no motivation to combine the teachings of Hartford with Estrada. Moreover, according to the

examples in Estrada, CT is an *antigen*, but according to Hartford, CT is an *adjuvant*. It is quite implausible that one of ordinary skill in the art would presume that an adjuvant (CT) in Estrada would require a further adjuvant when it already is an adjuvant. This contrary teaching of the references further precludes the combination asserted by the Examiner.

So again, even if proper, the combination of Timoney and Estrada with Hartford would not lead an ordinarily skilled artisan to the present invention, i.e., use of saponin in a mucosal *S. equi* vaccine, much less with an expectation of the commercial success the presently claimed vaccine has demonstrated (discussed further below). At best, the combination *might* teach use of saponin in a *S. equi* vaccine for administration by a route other than nasal mucosal administration, since Harford clearly discloses a preference for other adjuvants (CT or LT) for mucosal administration, and Estrada does not disclose that saponins, for their use as *adjuvants*, can be administered mucosally. However, there is clearly no teaching in any of the references that would provide the motivation to specifically combine a saponin with an unencapsulated *S. equi* specifically for nasal mucosal administration, much less, as discussed below, a reasonable expectation of success in doing so.

Accordingly, withdrawal of this rejection is respectfully requested.

2. The Examiner contends that one of ordinary skill in the art would have expected that combining saponin with the attenuated *S. equi* of Timoney would be successful based on the protective properties of the *S. equi* vaccines disclosed in Timoney and Hartford, and the beneficial results of the saponin adjuvant disclosed in Estrada.

Applicants respectfully disagree with this contention. According to this reasoning, Estrada could arguably be asserted to render obvious *any* vaccine disclosed in *any* patent which merely mentions that saponin is an adjuvant among other adjuvants. This is clearly not the correct law of obviousness, which further requires a motivation to combine references, and a reasonable expectation that the combination would be successful. The mere fact that references could be

combined does not make a claimed invention obvious in the absence of the motivation to make the combination. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-4 (Fed. Cir. 1992).

According to the PTO, there are 177 U.S. patents which claim vaccines and disclose saponin (among others) as one adjuvant (among others), and 35 U.S. patents which claim a vaccine with saponin specifically as an adjuvant, including a patent filed more than 30 years ago (U.S. 4,085,203). Clearly, the choice of adjuvant for any vaccine depends on factors other than the mere fact that the product is an adjuvant, including whether the adjuvant is effective with the particular vaccine product, e.g., an attenuated or killed microorganism or a soluble protein subunit; and whether the adjuvant is effective in the species to be vaccinated. Estrada sheds no light on either question with respect to the possible success of an attenuated *S. equi* vaccine for horses.

In the alternative, according to the Examiner's reasoning, the teachings of Hartford could be construed to render obvious vaccines comprising *any* eleven of the disclosed adjuvants, when combined with any other disclosure that taught the same or another vaccine. Again, this clearly would be an erroneous statement of the law of obviousness. A skilled artisan may have looked to Hartford or Estrada as a starting point to make a vaccine, but would have still been required to conduct undue experimentation to achieve a vaccine that was safe and effective for mucosal administration for preventing strangles in horses. As the Examiner knows, "obvious to try" is not the standard for *prima facie* obviousness under 35 U.S.C. §103. One must inquire whether the prior art would have suggested to one of ordinary skill in the art that the particular combination of elements with a reasonable expectation of success, viewed in light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *Id.* The Examiner's attention is further directed to the Federal Circuit's decision in *In re O'Farrell*, 853 F.2d

894, 7 USPQ2d 1673 (Fed. Cir. 1988). In particular, the court notes that there two ways to mistake "obvious to try" with obviousness. One is discussed below:

> In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

The Examiner has not met her burden of proving that use of saponin as an adjuvant would have been obvious ***and*** successful for an *S. equi* mucosal vaccine. The state of the art regarding vaccine preparation was not (and is not) as cut and dried as the Examiner presumes, but is quite unpredictable. Identification of a safe ***and*** effective vaccine entails more than merely combining the ingredients that others have used in other vaccines and "voila!" This is especially true with respect to the selection of appropriate adjuvants, namely saponin. For example, saponins have unpredictable adjuvant activity in humans, according to the disclosure in U.S. 5,817,314:

> Currently, aluminum hydroxide (alum) is the only available adjuvant approved for human use because of its low toxicity. Quil-A is, however, a mixture of a large number of homologous glycosides which may be represented by the general chemical structure wherein triterpenoid quillaic acid, the aglycone, is bonded to a sugar moiety of various type and length through a glycosidic linkage. It is also known that each of these glycosidic components displays widely varying adjuvant activity and toxicity, and therefore, Quil-A is not safe for use in pharmaceutical formulations for man (Kersten et al., Infect. Immun., 56, 432-438 (1988)). Accordingly, there have been attempts to identify only the safe and effective Quillaja saponin components and to develop a method for preparing thereof (emphasis not original).

It is not at all clear how the references overcome the same unpredictability in horses, with an attenuated *S. equi* vaccine. The references provide no clarification on this point, nor has the Examiner.

With no factual support for her position, the Examiner nevertheless did not consider the Li declaration persuasive on the issue of unpredictability of the effect of saponins as adjuvants in horses. Instead, the Examiner tried to shift the burden to Li by arguing that Li failed to evidence the ineffectiveness of saponin. The Examiner is respectfully reminded that the PTO bears the burden of establishing *prima facie* obviousness. Since the test for obviousness is a reasonable expectation of success, and Li provided an expert view on that issue, the Examiner must do more than offer unsupported arguments for obviousness.

In the absence of any actual experimental information about saponin's effectiveness as an adjuvant for intranasal vaccination of horses against *S. equi*, Li provided evidence of its unpredictability. While the presence of objective evidence would weigh in favor of non-obviousness, the lack of it does not weigh in favor of obviousness. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.,* 807 F.2d 955 (Fed.Cir.1986)). The Examiner has done nothing to refute Li's evidence. Accordingly, Applicants submit that the Li declaration, alone or in combination with the disclosure of U.S. 5,817,314, excerpted above, provides sufficient evidence of non-obviousness to use saponin as an adjuvant in horses for a vaccine against *S. equi.*

In further support of their argument of unpredictability, Applicants submit herewith an article by Jacobs et al., with **Hartford** as an author, (*Veterinary Record* 2000; 147:563-67; Exhibit 1), the TW 928 vaccine (deletion mutant as described in the Hartford patent application) was evaluated ***in horses*** via administration intranasally and intramuscularly, and intranasal administration failed to protect animals:

> In experiment 2, this mutant was tested as a vaccine by administering it by the intranasal and intramuscular routes. It was surprising that the intranasally vaccinated horses did not appear to be protected whereas the horses vaccinated intramuscularly were completely protected (page 566, col. 1, beginning third from last sentence).

This article continues by disclosing that some of the intranasal mutants, although attenuated and safe in mice, actually cause strangles in horses. According to the article, the only route of

administration that was successful using the deletion mutant vaccines was oral mucosal (page 566, col. 2, first paragraph). Moreover, use of saponin as an adjuvant is only disclosed in connection with the purified M-protein adjuvant (see page 563), not the deletion mutant. The authors concluded that since the intranasal vaccines were either safe but not protective, or caused strangles, that the optimal attenuation route for the intranasal route is "difficult to reach or does not exist at all."

In view of this teaching and the above arguments, Applicants assert that an obviousness argument cannot be sustained since it is clear that the prior art does **not** establish that saponin is suitable for any route of administration, for **any** *S. equi* vaccine. If use of saponin was obvious as of the filing date, in view of the teachings of Hartford, Timoney and Estrada, it remains a mystery that despite disclosing that saponin and 10 other agents could be used as adjuvants, Hartford herself *still* was not contemplating use of saponin with her *S. equi* vaccine three years following filing of her patent application (as the 2000 article demonstrates). Indeed, Hartford continued to fail to find an effective vaccine (which the claimed invention most certainly is, as discussed below) for nasal administration even after the filing date of this application. Hartford would presumably have been aware of saponin adjuvants, e.g., as disclosed in Estrada, which issued in 1997. Oddly, Hartford declined to use them – though according to the Examiner that would have been obvious. Accordingly, withdrawal of this rejection is respectfully requested.

3. According to the Examiner, Applicants have not demonstrated sufficient secondary indicia of unobviousness, e.g., commercial success and long-felt need, because Applicants have not supplied sufficient evidence that the Timoney strain is not effective commercially (e.g., the Daily declaration); and that the gross sales in comparison of a main competitor's product is not a sufficient assessment of total market share.

Applicants are admittedly stymied by this argument of lack of market share data. It appears that the Examiner is requesting that Applicants provide non-existent data in view of the fact that the Timoney vaccine is not, nor was ever, commercially available. However, if the Examiner so maintains, Applicants, in order to be compliant, will submit a declaration attesting to the fact that

the market share of the instant vaccine is significantly greater than the zero market share of the Timoney vaccine.

The Examiner also asserts that the commercial success cannot be attributed to the presence of saponin; and that prior art *S. equi* vaccines already solved the long-felt need. Again, Applicants respectfully disagree with this contention, which lacks any factual basis. Applicants have demonstrated sufficient secondary indicia of unobviousness, e.g., commercial success and long-felt need, via evidence that the Timoney strain is so ineffective commercially it was not commercialized.

There is no requirement to compare the commercial success of a product embodying the claimed invention with the closest prior art, Timoney. Applicants submit that possibly the Examiner is confusing the requirements of evidence of "commercial success" with evidence of "unexpected superior properties." While the *latter* requires comparison with the closest prior art, the former does not – indeed, in this case, cannot. As such, the commercial success demonstrated in the Daily Declaration should be accepted as *prima facie* evidence of unobviousness even in the absence of such a comparison.

With respect to the Examiner's failure to accord the evidence of commercial success with its appropriate weight, Applicants respectfully remind the Examiner of the Federal Circuit's stance on secondary indicia of unobviousness. In *Alco Standard Corp. v. Tennessee Valley Authority,* 1 USPQ.2d 1337 (1986), the Federal Circuit expressly held that the "secondary considerations" relating to obviousness, including commercial success, long-felt but unsolved needs, and failure of others, was an inquiry which is "...an essential and integral part of determining obviousness *vel non*" further citing other cases. The Federal Circuit has also held that:

> Evidence of secondary considerations may often be the most probative and cogent evidence of record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d at 1538-39, 218 USPQ at 879; see also *In re Piasecki,* 745 F.2d 1468, 223 USPQ 785 (Fed.Cir.1984).

Lastly, in opining about validity of a patent over an obviousness challenge, the Federal Circuit stated that:

> ...a determination that a patent challenger has carried its burden under §103, however, requires full consideration of any objective evidence of non-obviousness offered in rebuttal. That §103 issue cannot fairly be decided on only one party's part of the evidence (e.g., patent challenger's prior art) while disregarding the compelling impact of the other party's part (e.g., patentee's objective evidence). Nor is there warrant for singling out §103 as an area in which courts may disregard the probative force of any part of the evidence.

Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561 (Fed. Cir. 1987). Accordingly, Applicants respectfully request that the Examiner reconsider the evidence submitted in the Li and Daily declarations in view of the established law.

In further support of non-obvious, Applicants submit herewith several exhibits that show that Applicants' Pinnacle™ vaccine, which is an embodiment of the claimed invention (an attenuated *S. equi* with a saponin adjuvant) is the recommended and most widely used to date in the U.S. and Canada, and that this is due to the nasal administration made possible by the saponin adjuvant (as opposed to the aluminum hydroxide adsorbed suspension that is administered intramuscularly). To demonstrate this, Applicants submit another article, which quotes prior art inventor Timoney, as acknowledging that the Applicants' intranasal vaccine produces no adverse complications and appears to be protective in many horses. This article teaches that one caveat is that strangles can occur when the horses are administered the intranasal vaccine *concurrently* with the intramuscular vaccine, due to contamination from or improper handling of the needles for intramuscular injection (Grayson-Jockey Club Research 2002; 19(2): 1-4; Exhibit 2). As evidenced by the Pinnacle™ package insert (Exhibit 3) however, the Pinnacle™ vaccine does **not** require conjoint administration with the intramuscular vaccine.

Commercial success in North America is also supported by a report by the Canadian Ministry of Agriculture and Food, which reports that the Pinnacle™ vaccine, administered twice over 1 to 3 weeks, is more attractive than a killed, intramuscular vaccine since it produces the local antibodies necessary for protective immunity (Exhibit 4; page 2).

Lastly, an online report on a horse clinic in which vaccinations were discussed recites a recommendation from one veterinarian that horses should not be vaccinated against strangles, but further recommends that, if the owners decide to vaccinate, the intranasal vaccine (i.e., Applicants Pinnacle™) is "superior" to the intramuscular vaccine (Exhibit 5).

Regarding long-felt need, it is undisputed that where a product meets an unsolved need and is quickly adopted by the industry, that commercial success weighs against obviousness. *ATD Corp v. Lydall, Inc.* 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998). Applicants assert that if the prior art had solved the long-felt need, there would have been no reason to continue research and development for strangles vaccines after Timoney. Clearly, the facts establish otherwise, as demonstrated both by Hartford and the present invention. Recent publications, two abstracts of which are submitted herein (Exhibits 6 and 7), also contradict any such conclusion. These abstracts indicate that continued improvements to the Applicants' own Pinnacle™ vaccine (even by Timoney, who recognizes that his own patented strain works as a vaccine when combined with saponin in accordance with Applicants' invention, as shown in Exhibit 6), and new vaccines based on recombinant subunits (Exhibit 7). This is also contradicted by the length of time from the time the Timoney patent issued (1993) and the time Pinnacle™ achieved commercial success beginning in February 1998.

4. The Examiner contends that Applicants have not demonstrated that the *S. equi* vaccines in Hartford are not similarly protective to that of the present invention.

To rebut this, Applicants direct the Examiner's attention to the Veterinary Record article of which Hartford is an author (Exhibit 1) which blatantly demonstrates "from the horse's mouth" (pun intended) that intranasal administration of the Hartford vaccine is **not** protective. Further, while

pre-clinical studies with mice are valuable to evaluate the potential clinical safety and efficacy, this does not preclude the necessity for studies in the animal for which the drug will be approved and indicated. Since Hartford did not use saponin as an adjuvant in horses, much less for mucosal administration, there would be no conclusive results from doing comparative studies of the Hartford vaccine and that of the instant invention in horses or mice.

5. The Examiner asserts that the phrase "following *S. equi* challenge" is not supported in the specification.

To address this rejection, the Examiner's attention is respectfully directed to page 11, first and second full paragraphs, and page 15, second full paragraph, and page 16, lines 24-28. At page 11, the specifcation specifically discloses administration of a first dose of the vaccine and a booster dose 21 days later, followed by challenge with virulent *S. equi* 23 days following the booster (page 11). At page 15, the specification states that "the vaccinated horses were significantly protected against clinical disease as compared to the controls following a severe *S. equi* challenge." At page 16, the Conclusion indicates that "The composition of the invention satisfactorily protects vaccinated horses against a sever virulent *S. equi* challenge.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: October 26, 2004

Respectfully submitted,

By _____

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